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DOI: https://doi.org/10.1016/j.jfluchem.2019.02.003

Journal of Fluorine Chemistry, 30.01.2019-HH-3

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A novel access to 4-trifluoromethyl-1,3-thiazole derivatives via an intermediate thiocarbonyl ylide

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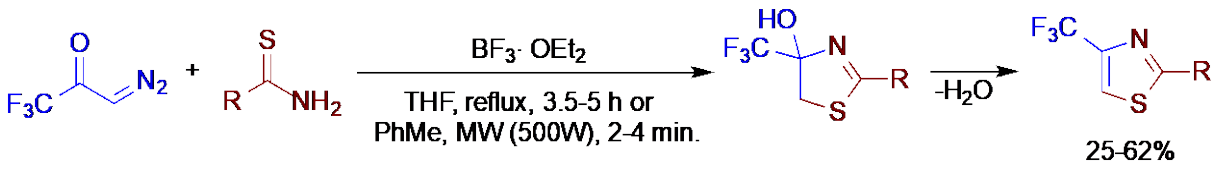
Abstract

A Lewis acid catalyzed reaction of trifluoroacetyldiazomethane (CF_3COCHN_2) with thiourea occurs in boiling THF solution in the presence of $BF_3{\cdot}OEt_2$ yielding 2-amino-4-trifluoromethyl-1,3-thiazole in a fair yield. Analogous reactions with aromatic thioamides, performed in the presence of a mesylchloride/triethylamine mixture as a dehydrating agent led to the corresponding 2-aryl-4-trifluoromethyl-1,3-thiazoles. Aromatic thioamides also react with CF_3COCHN_2 under MW irradiation, and after 2 min, the corresponding 1,3-thiazoles were obtained in fair yields. The obtained fluorinated 2-amino-1,3-thiazole was used for the reactions with selected *N*-alkylating and *N*-acylating reagents to give trifluoromethylated analogues of commonly known pharmaceuticals with 1,3-thiazole structures (Fanetizole and Lotifazole).

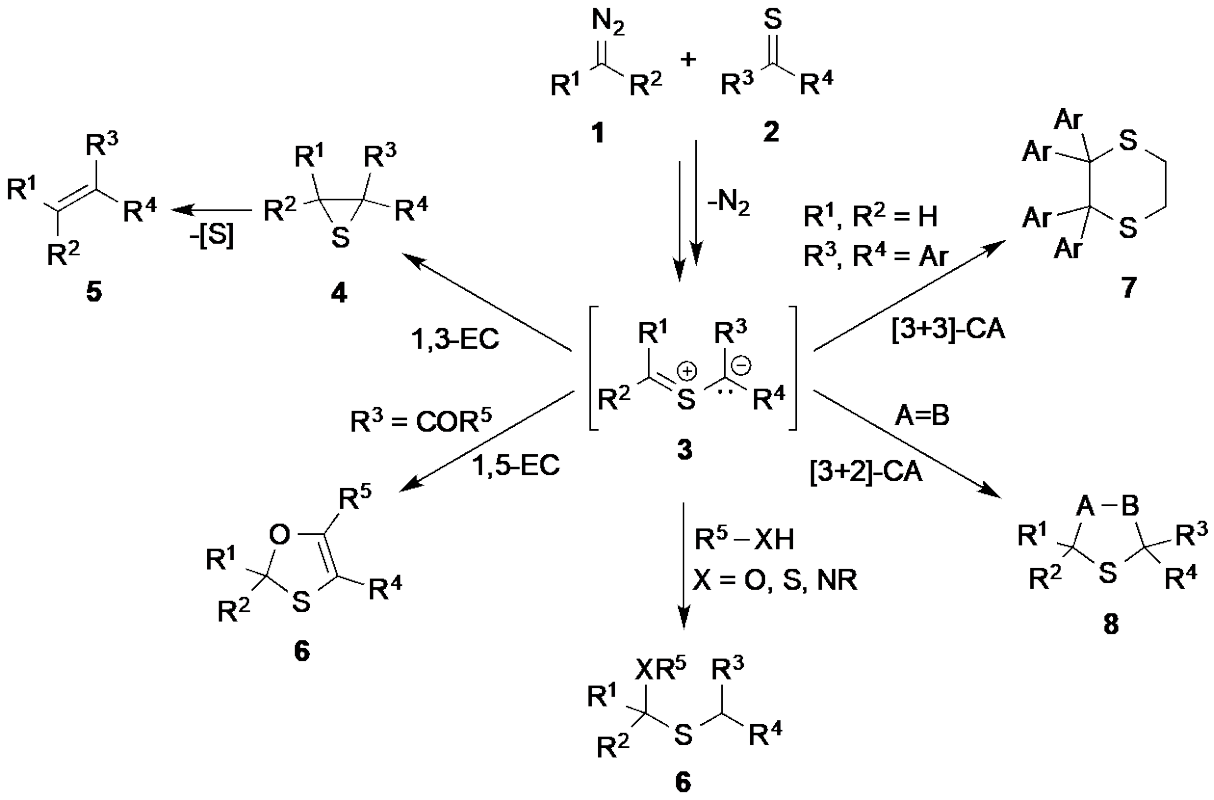
Keywords: Diazo compounds, 1,3-thiazoles, fluoroalkylated heterocycles, thioamides, boron trifluoride, thiocarbonyl ylides

Graphical abstract



1. Introduction

Reactions of diazo compounds **1** with thioketones **2** and other thiocarbonyl derivatives offer an attractive synthetic approach to more complex sulfur-containing and also sulfur-free products. They are formed in domino reactions, in which thiocarbonyl ylides **3** are the key intermediates. Depending on the substitution pattern of the starting materials, the '*in situ*' formed thiocarbonyl ylides can undergo diverse reactions such as 1,3- and 1,5-dipolar electrocyclization, [3+3]-dimerization, or [3+2]-cycloaddition with a suitable dipolarophile (Scheme 1). In addition, the trapping of the reactive intermediate with diverse nucleophiles is also known as inter- as well as intramolecular processes [1].



Scheme 1. Generation and typical reactions of the in situ generated thiocarbonyl ylides **3**.

Thiocarbonyl ylides **3** can be generated either via initial [3+2]-cycloaddition of a diazo and a thiocarbonyl compound, followed by N_2 elimination, or by the initial metal-catalyzed [1c,2] or microwave-assisted decomposition of the diazo compound **1** [3] and subsequent addition of the carbene formed thereby onto the sulfur atom of **2**.

The most reactive thiocarbonyl compounds are thioketones and thioesters. In contrast, thioamides are less reactive dipolarophiles and do not react with diazo compounds via the [3+2]-cycloaddition pathway. On the other hand, the most reactive diazo 1,3-dipoles are diazomethane (CH_2N_2) and its alkyl and aryl derivatives; the presence of an electron withdrawing carbonyl group in α-position substantially reduces their 1,3-dipolar reactivity [1d,2].

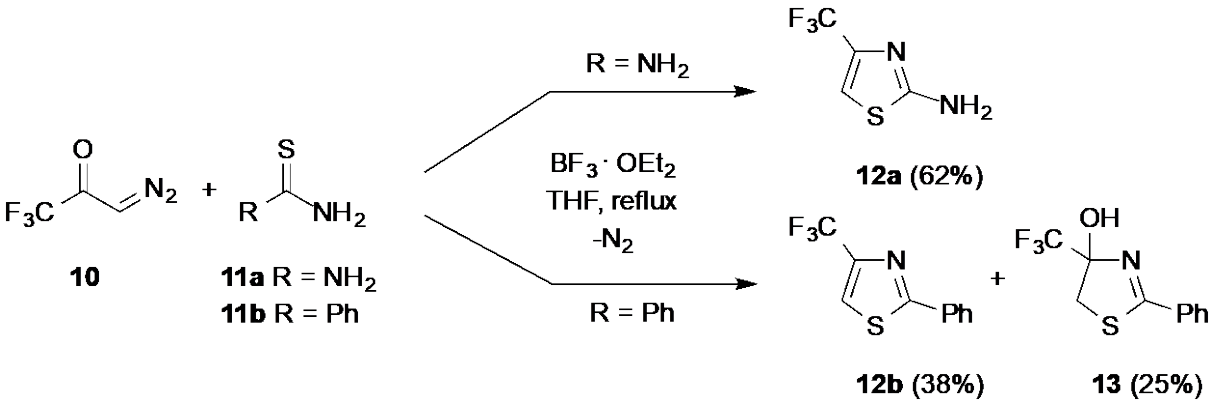
Among the five-membered aromatic sulfur heterocycles, 1,3-thiazoles are of great importance as biologically active compounds with a wide range of pharmaceutical applications [4]. One of the most important building blocks is 2-amino-1,3-thiazole, which is used for the preparation of diverse derivatives functionalized at the amino group [5]. For example, in a very recent publication, a multicomponent reaction for the synthesis of highly substituted 2-amino-1,3-thiazoles was reported [5c].

It is well documented that the introduction of a fluoroalkyl group modifies not only the physico-chemical properties of the organic compound but also contributes to the amplification of its biological activity [6]. In general, fluoroalkylated 1,3-thiazoles are rarely described, but 2-amino-4-trifluoromethyl-1,3-thiazole has already been reported [7], and it is recommended as a versatile synthon for the preparation of highly functionalized derivatives. The described syntheses are based on heterocyclization reactions starting with thiourea and 1,1,1-trifluoro-3-haloacetone [7a–c] or 1-phenylsulfonyl-1-trifluoromethyloxirane [7d,e].

The goal of the presented study was the elaboration of a new method for the synthesis of some 2-substituted 4-trifluoromethyl-1,3-thiazole derivatives, including the 2-amino representative, via a 'thiocarbonyl ylide approach'.

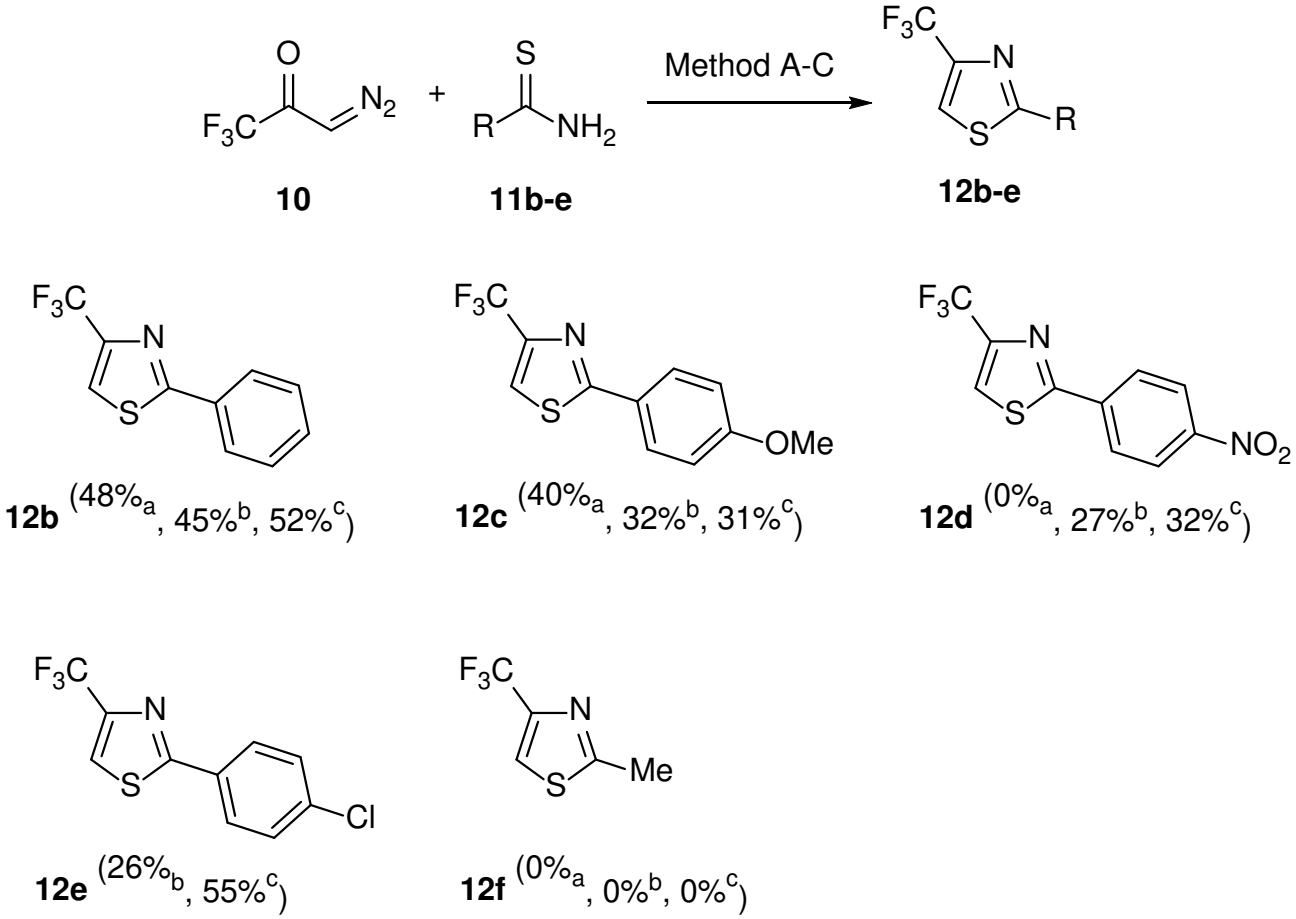
2. Results and discussion

In analogy to other acyldiazomethanes, 1-diazo-3,3,3-trifluoropropanone (**10**) was prepared according to the Arndt–Eistert method from trifluoroacetic acid anhydride (TFAA) and diazomethane (CH_2N_2) [8]. The test reactions aimed at the preparation of 2-amino- and 2-phenyl-4-trifluoromethyl-1,3-thiazoles **12a** and **12b** were carried out using the fluorinated α-diazoketone **10** and thiourea (**11a**) or thiobenzamide (**11b**), respectively. The reactions were performed in boiling, anhydrous tetrahydrofuran (THF) solution, in the presence of boron trifluoride etherate ($BF_3 \cdot OEt_2$) as a strong Lewis acid. Under these conditions, after 3.5–5 h the reaction was complete, and in the case of thiourea (**11a**), only one product was obtained in 35% yield. Based on spectroscopic data, its structure was elucidated as 2-amino-4-trifluoromethyl-1,3-thiazole (**12a**, Scheme 2). On the other hand, the experiment with thiobenzamide (**11b**) led to a mixture of two products identified as the expected 1,3-thiazole **12b** and its hydrated precursor **13**.



Scheme 2. Reaction of diazo compound **10** with thiourea (**11a**) and thiobenzamide (**11b**) in the presence of $BF_3{\cdot}OEt_2$ leading to 1,3-thiazoles **12**.

Based on these results, the reaction with **11b** was repeated and the crude reaction mixture was treated with phosphorus pentoxide (P_2O_5) or mesyl chloride (MsCl)/triethylamine (TEA) in order to dehydrate the initially formed product **13**. Under these conditions only compound **12b** was obtained in up to 48% yield (Scheme 3). Further optimization of the reaction conditions showed that 1,2-dimethoxyethane (DME) can be used as an alternative solvent and a comparable result was obtained with **11b** as in THF solution. The replacement of $BF_3{\cdot}OEt_2$ by other Lewis acids such as $Cu(OTf)_2$ in 1,2-dichloroethane (DCE) led again to mixtures of **12b** and **13**; the ratio of both products in the case of $Cu(OTf)_2$ was established to *ca.* 1:8 (total yield was 54%).



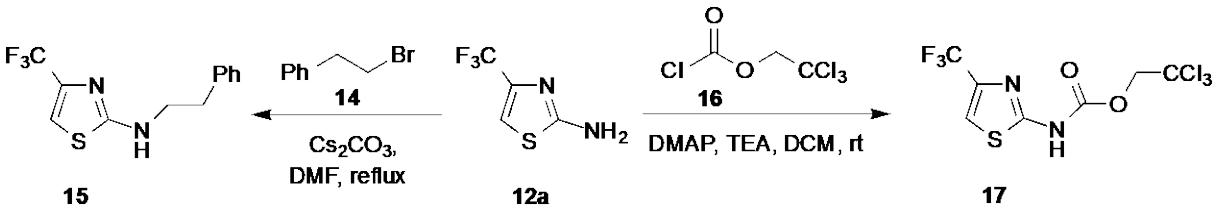
Scheme 3. Yields of 4-trifluoromethyl-1,3-thiazoles **12** prepared under different conditions ([a]Method A: (a) $BF_3{\cdot}OEt_3$, THF, reflux; (b) P_2O_5 dehydration; [b]Method B: (a) $BF_3{\cdot}OEt_3$, THF, reflux; (b) MsCl/TEA dehydration; [c]Method C: $BF_3{\cdot}OEt_3$, PhMe, MW (500W)).

The obtained results prompted us to check if corresponding carbonyl compounds, *i.e.* thiourea and benzamide, can be used in the reaction with **10** to give 1,3-oxazole derivatives. However, the experiments performed under the optimized conditions were unsuccessful.

Using the optimized conditions (THF, $BF_3{\cdot}OEt_2$, reflux; MsCl/TEA), reactions of **10** with 4-methoxy- and 4-nitrothiobenzamide (**11c**,**d**) were performed and the desired 1,3-thiazoles **12c** and **12d** were obtained in 32% and 27% yield, respectively (Scheme 3). Analogously, the reaction with 4-chlorothiobenzamide (**11e**) and P_2O_5 dehydration yielded **12e** in 26%. Unexpectedly, applying the same procedure for the reaction with thioacetamide afforded the expected 1,3-thiazole **12f** only in traces.

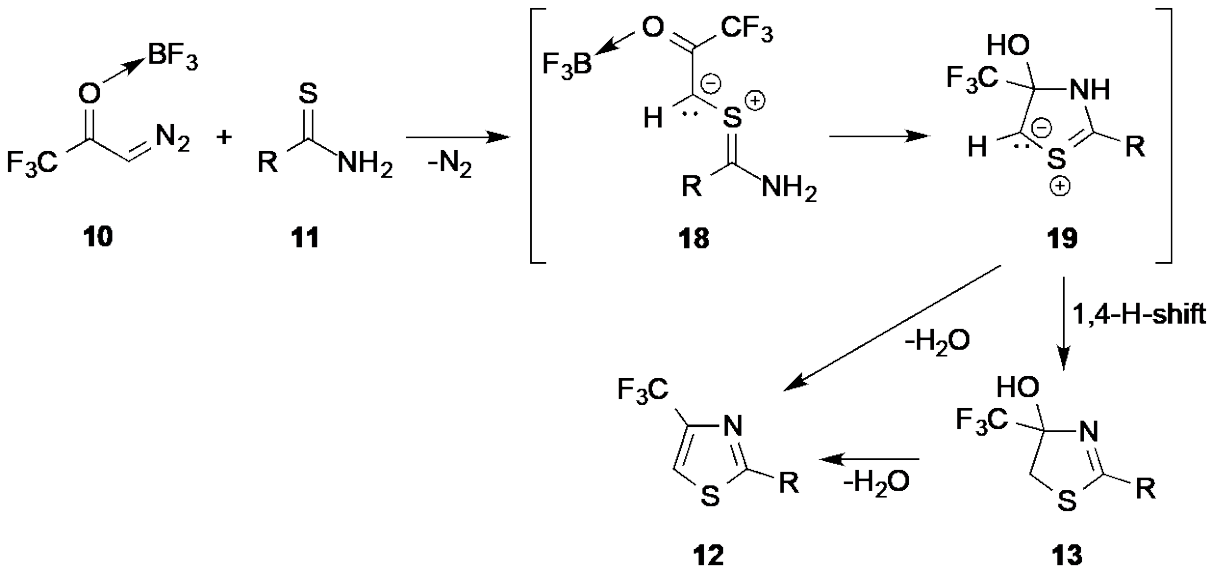
In a recent publication, reactions of hetaryl thioketones with less reactive α-diazoketones under microwave (MW) irradiation, leading to diverse products, have been reported [3]. In all cases, thiocarbonyl ylides were proposed as reactive intermediates. Prompted by these results, we decided to examine reactions of **10** with aromatic thioamides in a microwave reactor. To our delight, the test reaction with thiobenzamide (**11b**) performed in toluene in the presence of $BF_3{\cdot}OEt_2$ afforded after 2 min irradiation 1,3-thiazole **12b** in 52% yield. Similar results were obtained with **11c–e**, leading to the corresponding products **12c–e** in acceptable yields (Scheme 3). Unfortunately, the analogous syntheses of 2-amino- and 2-methyl-4-trifluoromethyl-1,3-thiazoles **12a** and **12f** under MW-irradiation were unsuccessful.

In the second part of this study, 2-amino-1,3-thiazole **12a** was converted into 2-*N*-functionalized derivatives by treatment with some electrophilic agents such as 1-bromo-2-phenylethane (**14**) and 2,2,2-trichloroethyl chloroformate (**16**), respectively. The corresponding products **15** and **17** were obtained in good yields, and in each case a trifluoromethylated analogue of an already known 1,3-thiazole-derived drug (Fanetizole and Lotifazole, respectively) [9] is represented (Scheme 4).



Scheme 4. *N*-Alkylations of 2-amino-1,3-thiazole **12a** leading to fluorinated analogues of already known bioactive compounds.

The mechanism of the reaction leading to 4-trifluoromethylated 1,3-thiazoles **12** requires a comment. Taking into account that thioamides, and especially thiourea, are known as very poor dipolarophiles, and fluorinated diazoketones belong to the less reactive 1,3-dipoles, a typical [3+2]-cycloaddition of **10** and **11** can be excluded as the initial step of the described reaction. Addition of $BF_3{\cdot}OEt_2$, acting as a strong Lewis acid, leads to activation of **10**, which is converted into a reactive species corresponding to an electrophilic carbene-type intermediate. The latter attacks the S-atom of the thioamide to give a thiocarbonyl ylide **18** (Scheme 5), very likely complexed with BF_3. This complexation may hinder the typical 1,5-dipolar electrocyclization of α-oxo thiocarbonyl ylides leading to 1,3-oxathiols **6** (Scheme 1). Instead, the activated carbonyl group is attacked by the NH_2 group to form the 1,3-thiazole skeleton in the intermediate **19**. The observed formation of product **13** occurs via 1,4-proton migration. A competitive pathway via dehydration of **19** leads to 1,3-thiazole **12**, which can also be formed via elimination of H_2O from compound **13**.



Scheme 5. Mechanistic explanation of the formation of 1,3-thiazoles **12** from diazo compound **10** and thioamides **11** via the intermediate thiocarbonyl ylide **18**.

3. Conclusions

The presented study shows a new methodology for the synthesis of 2-amino- and 2-aryl-4-trifluoromethyl-1,3-thiazoles via in situ-formed thiocarbonyl ylides. The reaction

occurs in the presence of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) as a strong Lewis acid, which activates the diazo compound and, very likely, prevents the expected 1,5-dipolar electrocyclization of the transient thiocarbonyl ylide leading to a 1,3-oxathiole. Instead, the intramolecular nucleophilic attack of the NH_2 group onto the activated carbonyl group results in the formation of the 1,3-thiazole. 2-Aryl-4-trifluoromethyl-1,3-thiazoles were also prepared from aromatic thioamides and CF_3COCHN_2 under MW irradiation for 2 min. Furthermore, the obtained trifluoromethylated 2-amino-1,3-thiazole was used as an attractive building block for the preparation of fluorinated analogues of some 1,3-thiazole-based pharmaceuticals.

4. Experimental

4.1. General information

Solvents and chemicals were purchased and used as received without further purification. Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), diethyl ether (Et_2O) and toluene (PhMe) were distilled over sodium/benzophenone(violet-coloured solution prior to use). Trifluoroacetic acid anhydride (TFAA), 2-(bromoethyl)benzene and 2,2,2-trichloroethylchloroformate were purchased from FluoroChem; sodium nitrite ($NaNO_2$) and thiourea were purchased from Avantor; thioamides **11a**–**e**, boron trifluoride etherate ($BF_3{\cdot}OEt_2$), and triethylamine (TEA) were purchased from Sigma-Aldrich (Merck). Obtained products were purified by standard column chromatography on silica gel (230–400 mesh, Merck) or FLASH column chromatography using Grace Reveleris X2 apparatus with UV–Vis and ELSD detection (commercially available 12 g or 24 g SiO_2 columns, pressure 20–25 psi, solvent flow rate 25–28 ml/min). Petroleum ether with increasing amounts of ethyl acetate (AcOEt) was used as eluent. Unless stated otherwise, yields refer to analytically pure samples. NMR spectra were recorded with Bruker Avance III 600 MHz (^{1}H NMR [600MHz]; ^{13}C NMR [151 MHz]; ^{19}F NMR [565 MHz]) instrument. Chemical shifts are reported in ppm relative to solvent residual peaks (^{1}H NMR: δ = 7.26 ppm [$CHCl_3$]; ^{13}C NMR: δ = 77.0 ppm [$CDCl_3$]). For detailed peak assignments 2D (HMQC) spectra were measured. IR spectra were measured with a FTIR NEXUS spectrometer (as KBr pellets). MS spectra were recorded on Varian 500 MS LS IonTrap spectrometer. Melting points were determined in capillaries with a Stuart SMP30 apparatus. Reactions under microwave conditions were carried out in CEM-Discover SP reactor.

*4.2. Synthesis of the 4-trifluoromethyl-1,3-thiazoles **12a-f***

Methods A and B: Reactions under thermal conditions - general procedure

Thiourea (**11a**) or an appropriate thioamide **11b–f** (1.0 mmol) was dissolved in anhydrous THF (1.0 ml), then $BF_3{\cdot}OEt_2$ (2.0 mmol, 0.25 ml) and 3-diazo-1,1,1-trifluoropropan-2-one (**10**, 1.2 mmol, 166 mg) were added. The solution was heated under reflux for 3.5–5 h (TLC control). After completion, the reaction was quenched with water and the product was extracted with dichloromethane (DCM) (4 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed '*in vacuo*'. Obtained compounds were separated and purified by standard column chromatography (SiO_2, eluent: petroleum ether with increasing amounts (up to 80%) of AcOEt.

*Method A: Dehydration of mixtures containing compounds of type **13** - reactions with P_2O_5 - general procedure*

The reaction mixture obtained with **11b–f** was dissolved in 0.5 mL DCM and then diluted with toluene (10 mL). Then, phosphorus pentoxide (P_2O_5) was added and the reaction mixture was heated under reflux. After 1 h, the mixture was neutralized with saturated, aqueous $NaHCO_3$ solution and extracted with DCM (4 x 15 mL), the combined organic phases were dried over anhydrous Na_2SO_4, the drying agent was filtered off, and the solvents were evaporated at reduced pressure. Obtained products were purified by standard column chromatography (SiO_2, eluent: petroleum ether with increasing amounts (up to 30%) of AcOEt.

*Method B: Dehydration of mixtures containing compounds of type **13** - reactions with mesyl chloride (MsCl) and triethylamine (TEA) - general procedure*

The reaction mixture obtained with **11b–f** was dissolved in anhydrous DCM (25 mL), mesyl chloride (MsCl, 1.2 equiv., 1.2 mmol, 138 mg) and triethylamine (TEA, 2.5 equiv, 2.5 mmol, 252 mg) were added while dissolved in DCM (~ 1 mL) and the reaction mixture was heated at reflux for 1 h. Then, the mixture was neutralized with saturated, aqueous $NaHCO_3$ solution and extracted with DCM (4 x 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was

evaporated '*in vacuo*'. The obtained crude products were purified by column chromatography (SiO_2, eluent: petroleum ether with increasing amounts (up to 30%) of AcOEt.

Method C: Reactions under MW irradiation - general procedure

An appropriate thioamide **11b–f** (1.0 mmol) was dissolved in anhydrous toluene (5 mL), then $BF_3{\cdot}OEt_2$ (2.0 mmol, 0.25 ml) and **10** (1.2 mmol, 166 mg) was added. The solution was placed in a microwave reactor and heated to 150 °C. After 2−4 min irradiation, the reaction was quenched with water and the product was extracted with DCM (4 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed '*in vacuo*'. Obtained compounds were separated and purified by column chromatography (SiO_2, eluent: petroleum ether with increasing amounts (up to 30%) of AcOEt.

*4.2.1. 4-(Trifluoromethyl)-1,3-thiazol-2-amine (**12a**)*

Yield: Method A: 104 mg (62%). Colourless crystals, mp 65–67 °C (PE/DCM; [9]: 68−69.5 ºC). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.55 (s, 2H, NH_2), 6.95 (s, 1H, CHthiazole). ^{13}C-NMR: δ = 110.2 (q, $^3J_{C,F}$ = 4.5 Hz, CHthiazole), 120.2 (q, $^1J_{C,F}$ = 268.5 Hz, CF_3), 140.4 (q, $^2J_{C,F}$ = 37.5 Hz, *C*CF_3), 169.1 (C(2) thiazole). ^{19}F NMR ($CDCl_3$, 565 MHz): δ = –65.21 (CF_3). IR (KBr): ν 3287*w*, 3123*br.w* (NH), 1668*w*, 1627*m*, 1533*m*, 13736*m*, 1231*s*, 1172–1055*vs* (CF_3), 922*s*, 836*m* cm^{-1}. ESI-(+)-MS: m/z 169 (100, $[M+H]^+$); ESI-(–)-MS: m/z 167 (100, $[M–H]^–$). EA calcd. for $C_4H_3F_3N_2S$ (229.22): C 52.40, H 2.64, N 6.11; found: C 52.27, H 2.41, N 6.26.

*4.2.2. 2-Phenyl-4-(trifluoromethyl)-1,3-thiazole (**12b**)*

Yield: Method A: 110 mg (48%); Method B: 103 mg (45%); Method C:119 mg (52%). Colourless crystals, mp 48–49 °C (PE). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.45–7.50 (m, 3H, Ph), 7.73 (s, 1H, CHthiazole), 7.97–7.99 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 120.5 (q, $^3J_{C,F}$ = 3.0 Hz, CHthiazole), 120.8 (q, $^1J_{C,F}$ = 268.5 Hz, CF_3), 127.2, 129.4, 131.3 (5CH, Ph), 132.8(1C, Ph), 146.0 (q, $^2J_{C,F}$ = 36.0 Hz, *C*CF_3), 170.8 (C(2) thiazole).^{19}F NMR ($CDCl_3$, 565 MHz): δ = –64.01 (CF_3). IR (KBr): ν 3144*w*, 1630*w*, 1465*m*, 1440*m*, 1366*m*, 1230*m*, 1118–1083*s* (CF_3), 984*m*, 903*m*, 732*m* cm^{-1}. ESI-(+)-MS: m/z 230 (100, $[M+H]^+$). EA calcd. for $C_{10}H_6F_3NS$ (168.14): C 28.57, H 1.80, N 16.66; found: C 28.86, H 1.96, N 16.92.

*4.2.3. 4,5-Dihydro-2-phenyl-4-(trifluoromethyl)-1,3-thiazol-4-ol (**13**)*

Yield: Method A: 61 mg (25%). Colourless crystals, mp 129–131 °C (PE/DCM). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.43–7.46 (m, 2H, Ph), 7.54–7.56 (m, 1H, Ph), 7.87–7.86 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 38.1 (CH_2), 105.8 (q, $^{2}J_{C,F}$ = 30.0 Hz, *C*CF_3), 123.5 (q, $^{1}J_{C,F}$ = 283.5 Hz, CF_3), 128.9, 129.0, 133.0 (5CH, Ph), 131.9 (1C, Ph), 177.6 (C(2) thiazole). ^{19}F NMR ($CDCl_3$, 565 MHz): δ = 82.63 (CF_3). IR (KBr): *v* 3107*br.m* (OH), 2799*w*, 1600*m*, 1564*m*, 1493*w*, 1450*w*, 1322*m*, 1253*s*, 1179*vs* (CF_3), 1060*m*, 1010*s*, 1000*m*, 955*w* cm^{-1}. ESI-(+)-MS: m/z 248 (100, $[M+H]^+$). EA calcd. for $C_{10}H_8F_3NOS$ (247.24): C 48.58, H 3.26, N 5.67; found: C 48.52, H 3.09, N 5.66.

*4.2.4. 2-(4-Methoxyphenyl)-4-(trifluoromethyl-1,3-thiazole (**12c**)*

Yield: Method A: 104 mg (40%);Method B: 83mg (32%);Method C:80mg (31%). Pale-yellow crystals, mp 50–51 °C (PE/DCM). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.87 (s, 3H, Me), 6.95–6.97 (m, 2 arom. H), 7.65 (s, 1H, CH thiazole), 7.90–7.92 (m, 2 arom. H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 55.4 (Me), 114.4, 128.4 (4 arom. CH), 119.2 (q, $^{3}J_{C\text{-}F}$ = 7.0 Hz, CH thiazole), 120.5 (q, $^{1}J_{C,F}$ = 268.7 Hz, CF_3), 125.5, 161.9 (2 arom. C), 145.4 (q, $^{2}J_{C,F}$ = 37.5 Hz, *C*CF_3) 170.3 (C(2) thiazole). ^{19}F NMR ($CDCl_3$, 565 MHz): δ = –64.04 (CF_3). IR (KBr): *v* 3128*w*, 2941*w*, 2893*w*, 1577*s*, 1534*m*, 1522*m*, 1462*vs*, 1438*s*, 1417*s*, 1362*s*, 1181–1156*vs* (CF_3), 1127*vs*, 1079*vs*, 1024*vs*, 983*s*, 907*vs* cm^{-1}. ESI-(+)-MS: m/z 260 (100, $[M+H]^+$). EA calcd. for $C_{11}H_8F_3NOS$ (259.25): C 50.96, H 3.11, N 5.40; found: C 50.94, H 2.94, N 5.51.

*4.2.5. 2-(4-Nitrophenyl)-4-(trifluoromethyl-1,3-thiazole (**12d**)*

Yield: Method B: 74 mg (27%); Method C: 88 mg (32%). Orange crystals, mp 131–133 °C (PE/DCM). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.89 (s, 1H, CH thiazole), 8.16–8.18 (m, 2 arom. H), 8.32–8.34 (m, 2 arom. H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 120.6 (q, $^{1}J_{C,F}$ = 268.5 Hz, CF_3), 122.6 (q, $^{3}J_{C,F}$ = 3.0 Hz, CH thiazole), 124.9, 128.0 (4 arom. CH), 138.2, 149.6 (2 arom. C), 147.1 (q, $^{2}J_{C,F}$ = 39.0 Hz, *C*CF_3), 167.8 (C(2) thiazole).^{19}F NMR ($CDCl_3$, 565 MHz): δ = –64.03 (CF_3). IR (KBr): *v* 3104*m*, 1598*m*, 1521*vs*, 1456*m*, 1406*w*, 1320*vs*, 1235*vs*, 1182*vs* (CF_3), 1136*vs,* 991*s*, 904*m* cm^{-1}. ESI-(+)-MS: m/z 274 (100, $[M]^+$). EA calcd. for $C_{10}H_5F_3N_2O_2S$ (274.22): C 43.80, H 1.84, N 10.22; found: C 43.71, H 1.83, N 10.50.

*4.2.6. 2-(4-Chlorophenyl)-4-(trifluoromethyl-1,3-thiazole (**12e**)*

Yield: Method B: 69 mg (26%); Method C: 145 mg (55%). Colourless crystals, mp 50–52 °C (PE/DCM). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.44–7.45 (m, 2H, Ph), 7.75 (s, 1H, CH thiazole), 7.91–7.92 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 120.6 (q, $^{1}J_{C,F}$ = 268.5 Hz, CF_3), 120.7 (q, $^{3}J_{C,F}$ = 3.0 Hz, CH thiazole), 128.3, 129.6 (4 arom. CH), 131.2, 137.4 (2 arom. C), 146.1 (q, $^{2}J_{C,F}$ = 36.0 Hz, *C*CF_3), 169.3 (C(2) thiazole). ^{19}F NMR ($CDCl_3$, 565 MHz): δ =–64.06 (CF_3). IR (KBr): *v* 3101*w*, 1597*w*, 1533*w*, 1457*s*, 1400*m*, 1250*m,* 1228*s*, 1172–1125*vs* (CF_3), 985*s,* 728*m* cm^{-1}. ESI-(+)-MS: m/z 264 (100, $[M+H]^+$), 266 (40, $[M+H]^+$). EA calcd. for $C_{10}H_5ClF_3NS$ (263.66): C 45.55, H 1.91, N 5.31; found: C 45.78, H 2.16, N 5.16.

*4.3. Alkylation of 2-amino-4-trifluoromethyl-1,3-thiazole (**12a**) – Synthesis of compound **15***

2-Amino-4-trifluoromethyl-1,3-thiazole (**12a**, 0.5 mmol, 84 mg) was dissolved in anhydrous DMSO (3.0 mL), then 2-(bromoethyl)benzene (**14**, 1.5 mmol, 278 mg) and cesium carbonate (2.5 mmol, 815 mg) were added. This solution was heated at 80 °C for 2 h. Then it was extracted with DCM (4x15mL), the organic phases were combined and dried over anhydrous Na_2SO_4, and the solvent was evaporated '*in vacuo*'. The obtained product was purified by standard column chromatography (SiO_2, eluent: petroleum ether with increasing amounts (up to 20%) of AcOEt). It was crystallized from a mixture of hexane, heptane and DCM by slow evaporation of the solvent.

*N-Phenylethyl-4-(trifluoromethyl)-1,3-thiazol-2-amine (**15**).* Yield: 53 mg (39%). Colourless crystals, mp 120–121 °C (PE/DCM). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.95–2.97 (t, 2H, CH_2), 3.53–3.56 (q, 2H, CH_2NH), 5.63 (brs, 1H, NH), 6.92 (s, 1H, CH thiazole), 7.22–7.27 (m, 3H, Ph), 7.32–7.34 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 35.3 (CH_2), 47.3 (CH_2NH), 108.2 (q, $^{3}J_{C,F}$ = 4.5 Hz, CH thiazole), 120.4 (q, $^{1}J_{C,F}$ = 268.5 Hz, CF_3), 127.2, 129.4, 131.3 (5CH, Ph), 132.8 (1C, Ph), 141.0 (q, $^{2}J_{C,F}$ = 157.5 Hz, *C*CF_3), 170.8 (C(2) thiazole). ^{19}F NMR ($CDCl_3$, 565 MHz): δ = –64.06 (CF_3). IR (KBr): *v* 3222*w* (NH), 3116*w*, 2993*w*, 2918*w*, 2861*w*, 1604*m*, 1377*m*, 1235*m*, 1156–1121*vs* (CF_3), 1071*m*, 1007*w*, 918*w* cm^{-1}. ESI-(–)-MS: m/z 260 (100, $[M–CH_2CH_2Ph]^–$). EA calcd. for $C_{12}H_{11}F_3N_2S$ (272.29): C 52.93, H 4.07, N 10.29; found: C 52.85, H 3.86, N 10.38.

*4.4. Acylation of 2-amino-4-trifluoromethyl-1,3-thiazole (**12a**) – Synthesis of compound **17***

2-Amino-4-trifluoromethyl-1,3-thiazole (**12a**, 0.5 mmol, 84 mg) was dissolved in anhydrous DCM (3 mL), then 2,2,2-trichloroethyl chloroformate (**16**, 0.75 mmol, 159 mg), triethylamine (TEA, 0.55 mmol, 87.5 mg) and 4-dimethylaminopyridine (DMAP, 0.05 mmol, 6 mg) were added. This solution was stirred initially at 0 °C for 45 min, then warmed to room temperature and stirred for 12 h. Then, the reaction mixture was washed with saturated, aqueous $NaHCO_3$ solution and water. The product was extracted with DCM (4x10 mL). The organic layers were collected and dried over anhydrous Na_2SO_4 and the organic solvent was evaporated under reduced pressure. The obtained product was purified by standard column chromatography (SiO_2, eluent: petroleum ether with increasing amounts (up to 20%) of AcOEt). It was crystallized from a mixture of hexane, heptane and DCM by slow evaporation of the solvent.

*2,2,2-Trichloroethyl-N-[4-(trifluoromethyl)thiazol-2-yl]carbamate (**17**).* Yield: 154 mg (90%). Colourless crystals, mp 118–120 °C (PE). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.89 (s, 2H, CH_2), 7.41 (s, 1H, CH thiazole), 8.77 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 75.4 (CH_2), 94.3 (CCl_3), 115.7 (q, $^3J_{C,F}$ = 3.0 Hz, CH thiazole), 120.3 (q, $^1J_{C,F}$ = 268.5 Hz, CF_3), 140.3 (q, $^2J_{C,F}$ = 37.5 Hz, *C*CF_3) 151.6 (C(2) thiazole), 160.0 (C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ = –64.58 (CF_3). IR (KBr): *v* 3188*br.m* (NH), 3076*m*, 2968*m*, 2789*w*, 1748*vs* (C=O), 1567*vs*, 1458*m*, 1374*s*, 1289*vs*, 1147–1110*vs* (CF_3), 923*vs* cm^{-1}. ESI-(–)-MS: m/z 341 (100, [M–H]$^-$), 343 (43, [M–H]$^-$). EA calcd. for $C_7H_4Cl_3F_3N_2O_2S$ (343.53): C 24.57, H 1.17, N 8.15; found: C 24.49, H 1.32, N 8.22.

Acknowledgements

This work is a part of the M.Sc. thesis of M. Błaszczyk, University of Łódź (2018). Financial support by the National Science Center (Poland, Cracow) Grant PRELUDIUM–8 (project number 2014/15/N/ST5/02895)) is gratefully acknowledged.

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